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# CONTRIBUTION TO THE STUDY OF THE ACTION OF THE ADRENOCORTICAL GLANDS ON THE PRODUCTION OF GASTRIC ULCERATIONS IN THE RAT BY PROLONGED IMMOBILITY

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16. Abstract A series of experiments were carried out on male rats, restrained by a special system of immobilization for 24 hr. Weight variations and the mortality rate were investigated, as well as the ulcerated gastric area and urinary eliminations of uropepsin, 17-ketosteroids and 17-hydroxycorticosteroids. Intact animals subjected to immobilization had a mortality of 11%. Immobilization of the adrenalectomized animals induced a mortality of 44%, whereas immobilization combined with the administration of cortisone (16 mg/kg body weight) permitted survival of all animals. Gastric lesions were produced in 78% of the immobilized animals (mean ulcerated surface = 4.84 $mm^2$). This increased to 100% in animals subjected to immobilization associated with cortisone (mean ulcerated surface = 3.27 $mm^2$) and dropped to 44% in adrenalectomized and immobilized rats (mean ulcerated surface = 0.9 $mm^2$). None of the controls (rats not immobilized but kept on a fasting diet for the duration of the experiment) exhibited any lesions of the gastric mucosa. Control rats eliminated 9.21 u.p./24 hr of uropepsin, 0.051 mg 17-ketosteroids/24 hr and 0.039 mg 17-hydroxycorticosteroids/24 hr.

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# CONTRIBUTION TO THE STUDY OF THE ACTION OF THE ADRENOCORTICAL GLANDS ON THE PRODUCTION OF GASTRIC ULCERATIONS IN THE RAT BY PROLONGED IMMOBILITY

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Rossi and Bonfils [15] have shown that forced immobilization /307* of rats leads to gastric ulcerations whose frequency increases with the duration of constraint.

Many studies have been devoted to the mechanism of these disorders.

A number of authors have investigated the role of the endocrine glands, especially of the pituitary and adrenal glands.

Thus, Brodie [7], Menguy [13] and Bonfils [5] studied the influence of hypophysectomy. These authors agree that this operation does not prevent the appearance of gastric ulcerations. Bonfils [5] even remarks that hypophysectomy has a clear aggravating effect.

Studies of adrenalectomy have resulted in contradictory data. For some authors (Brodie [7], Martindale [12]) adrenalectomy has aggravating effects; for others (Bonfils, et al. [3]) it causes no differences as compared with normal animals.

Nor is the study of urinary elimination of corticosteroids (Simler et al. [16]) conclusive.

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* Numbers in the margin indicate pagination in the foreign text.

The importance of the adrenal glands in gastrosecretory homeostasis [9], as well as the contradictory data in the literature, inspired us to reexamine the influence of these glands in the course of forced immobilizations of animals.

At the same time, we deemed it useful to study, in addition to the role of adrenalectomy and elimination of 17-ketosteroids and uropepsin, the effect of cortisone and urinary elimination of 17-hydroxycorticosteroids.

## Methods and Materials

The experiments involved 89 male white rats with an average weight of 160 g. Gastric ulcerations were caused by immobilization of the rats for 24 hours according to a method similar to that of Selye (cited by [6]).

The animals were divided into the following groups: /308

Group I. Normal animals, part of which received ordinary food while another part were kept on a fast similar to that of the rats subjected to immobilization.

Group II. Animals subjected to immobilization for 24 hours.

Group III. Animals injected with 5 mg/100 g body weight of cortisone 1 day before and during immobilization, at a 12-hour interval.

Group IV. Animals subjected to immobilization 7 days after bilateral adrenalectomy.

The animals subjected to immobilization were deprived of food 17-18 hours before as well as during immobilization. Immediately

after fixation on the table the animal was injected subcutaneously with 5 ml of isotonic solution of sodium chloride.

All animals were weighed before and after immobilization. The mortality was investigated, and after sacrifice through decapitation, the gastric mucosa was examined in order to determine the appearance of ulcerations and their surface. After appropriate processing histologic examination of the stomach was also effected.

The uropepsin, 17-ketosteroids and 17-hydroxycorticosteroids were measured in a 24-hour specimen of urine from the normal animals, both fed and unfed (group I), as well as in the animals subjected to simple immobilization (group II).

The urinary steroids were determined by the method of Zimmerman in the case of the 17-ketosteroids and the method of Porter Silber in the case of the 17-hydroxycorticosteroids, and the results were expressed in mg/24 hours. The uropepsin was determined by the method of Anson-Mirsker-Gray, and the results were expressed in peptic units for 24 hours.

## Results

It follows from our results that the mean weight reduction was approximately the same for the normal animals deprived of food, those subjected to simple immobilization or those which, in addition, were adrenalectomized beforehand (mean 7%). The weight reduction was more pronounced in animals in which immobilization was associated with administration of cortisone (10.6 g%) (Fig. 1).

The mortality was 11% in the animals subjected to simple immobilization and rose to 44% in those which had also been adrenalectomized beforehand. All the normal animals, as well as

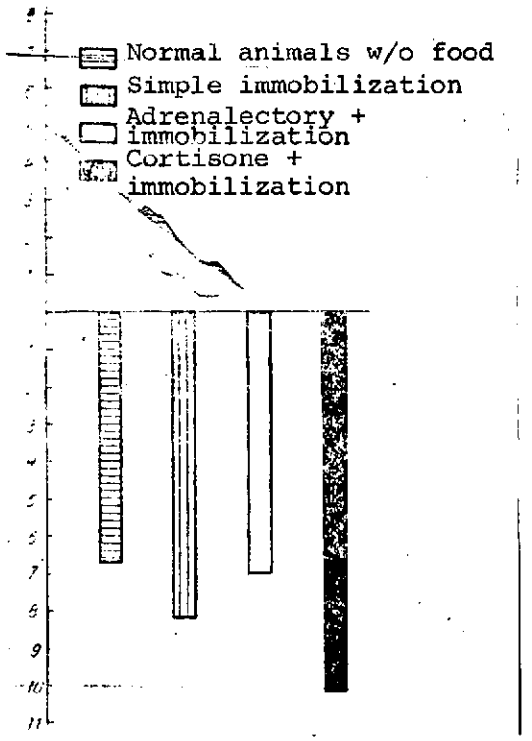


Fig. 1. Mean weight reductions.

those to which, in addition to immobilization, cortisone was administered, survived (Fig. 2).

Table I shows the results for urinary elimination of uropepsin, 17-ketosteroids and 17-hydroxy-corticosteroids.

There exist significant statistical differences in the sense of a reduction in the quantity of uropepsin eliminated in normal animals on a fasting diet as compared with fed animals (9.82 ± 5.70 as compared with 20.24 ± 7.13 u.p. for 24 hours; $p < 0.01$). A significant reduction was also ascertained in animals subjected to constraint as compared with animals on a fasting diet (198 ± 0.84 as compared with 9.82 ± 5.70 u.p. for 24 hours; $p < 0.01$) (Fig. 3).

Elimination of 17-ketosteroids showed no significant variations between normal fed animals (0.060 ± 0.019 mg/24 hours) and those kept on a fasting diet (0.051 ± 0.006 mg/24 hours; $p < 0.10$); in the animals subjected to immobilization, though an increase was found in the mean values eliminated (0.067 ± 0.041 mg/24 hours) in comparison with the rats kept on a fasting diet, statistical calculations nevertheless showed that the differences are not significant ($p > 0.10$) (Fig. 4).

Nor did elimination of 17-hydroxycorticosteroids show significant differences between normal fed animals (0.044 ± 0.025 mg/24 hours) and those kept on a fasting diet (0.050 ± 0.032 mg/24 hours;

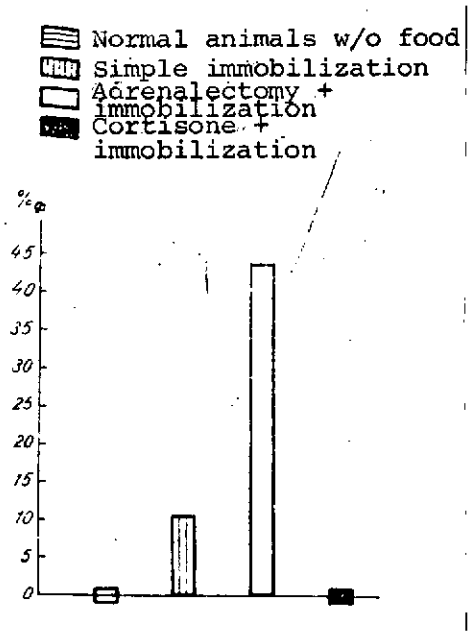


Fig. 2. Mean of mortality.

p < 0.10); on the other hand, under the influence of constraint, elimination of 17-hydroxycorticosteroids dropped to a mean value of 0.011 ± 0.002 mg/24 hours, a significantly more reduced quantity as compared with the value found in normal animals kept on a fasting diet (p < 0.01) (Fig. 5). /310

As far as the appearance of gastric ulcerations is concerned, we found that none of the normal animals (fed or on a fasting diet) showed any ulcerating lesions.

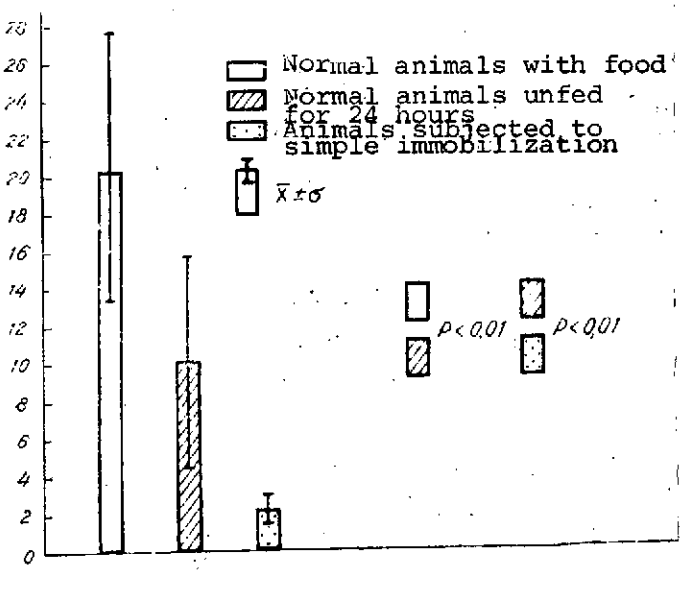


Fig. 3. Urinary elimination of uropepsin in normal white rats or rats subjected to forced immobilization for 24 hours (mean values).

In the other experimental groups, gastric ulcerations appeared in 78% of the animals subjected to immobilization, dropped to 44% in the animals adrenalectomized beforehand but rose to 100% in the animals to which, in addition to immobilization, cortisone was administered (Fig. 6).

The ulcerated surface was on the average 4.84 $mm^2$ in animals subjected to constraint,

TABLE 1. URINARY ELIMINATION OF UROPEPSIN, 17-KETOSTEROIDS, AND 17-HYDROXYCORTICOSTEROIDS (17-OH) IN NORMAL WHITE RATS OR RATS SUBJECTED TO FORCED IMMOBILIZATION FOR 24 HOURS (MEAN VALUES ±σ)

| Exp. No. | Group | Up/24 hr | 17-CS (mg/24 hr) | 17-OH (mg/24 hr) |
|---|---|---|---|---|
| 1 | Normal animals with food | 20.24±7.13 | 0.060 0±0,019 5 | 0.044±0.025 |
| 2 | Normal animals unfed for 24 hours | 9.82±5.70 | 0.051 0±0,006 5 | 0.050±0.032 |
| 3 | Animals subjected to simple immobilization | 1.98±0,84 | 0.067 0±0,041 4 | 0.011 3±0,003 8 |
| Statistical significance | | 1 : 2 t = 5,41 p<0,01<br>2 : 3 t = 4,63 p < 0,01 | 1 :2 t = 0,32 p > 0,1<br>1 : 3 t = 0,11 p > 0,1 | 1 : 2 t = 0,61 p > 0.10<br>2 : 3 t = 1,22 p > 0,01 |

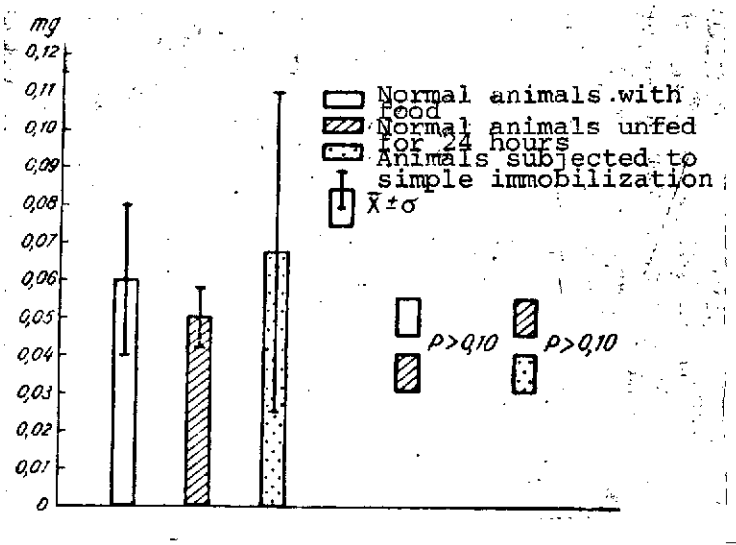


Fig. 4. Urinary elimination of 17-ketosteroids in normal white rats or rats subjected to forced immobilization for 24 hours (mean values).

3.27 $mm^2$ in animals to which cortisone had been administered and 0.9 $mm^2$ in rats adrenalectomized beforehand (Fig. 7).

Regardless of the experimental group, gastric ulcerations were found only in the glandular part of the stomach. Against the background of a purpuric mucosa, ulcerations appear in the form of darkish hemorrhagic spots, often multiple and sometimes surrounded by an edematous areola (Fig. 8).

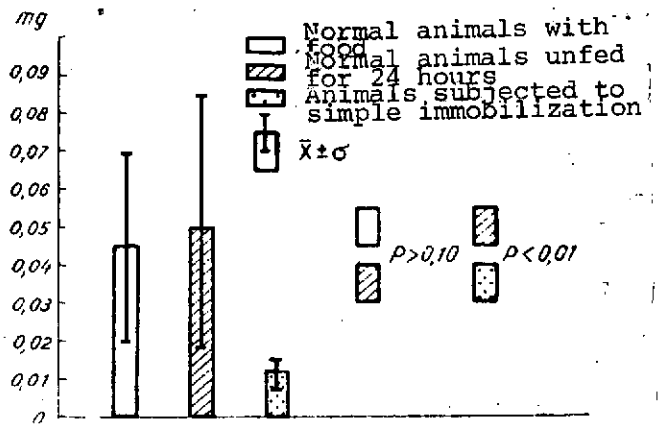


Fig. 5. Urinary elimination of 17-hydroxysteroids in normal white rats or rats subjected to forced immobilization for 24 hours (mean values)

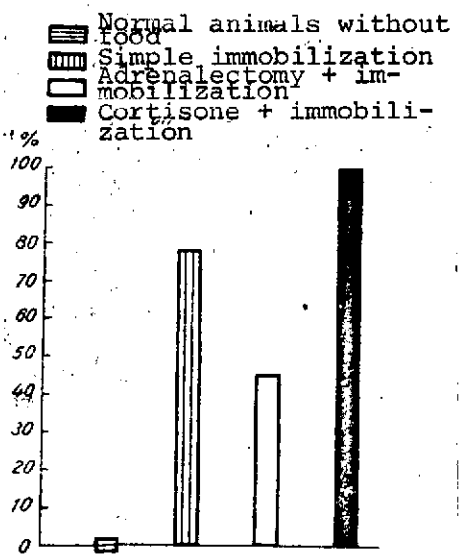


Fig. 6. Proportion of animals with ulcerations.

Under microscopic examination the gastric mucosa shows an intense capillary vasodilation, which is sometimes confluent with a hemorrhagic appearance. The loss of substance is in general superficial, rarely exceeding the muscularis mucosae (Fig. 9).

## Discussion

Our results confirm the studies in the literature about the possibility of producing gastric ulcerations in the white rat through forced immobilization [1, 2, 4, 8, 15] and furnishes some new data about the mechanism involved in producing them.

Our investigations indicate that the immobilized animals' mean weight reduction (8%) is due for the most part to a 24-hour fast. Such weight losses were observed in normal animals subjected only to a fast (6.7%), as well as in those immobilized after adrenalectomy (7%). Administration of /311 cortisone, on the other hand, by intensifying protein catabolism, reduced the rats' weight by an average of 10% from the initial value.

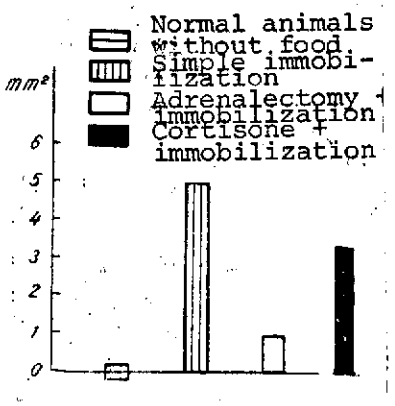


Fig. 7. Mean surface of ulcerations.

Fig. 8. Macroscopic appearance of gastric ulcerations appearing in the glandular zone.

As did Bonfils et al. [3], we observed the appearance of gastric ulcerations in most of the animals. On the other hand, the mortality in our experiments (11%) was greater than that in the case of Bonfils et al. (5.3%).

As regards the participation of the adrenal glands in the evolution of the gastric changes or of the urinary elimination of corticosteroids produced by forced immobilization, our results agree only in part with those in the literature.

We believe that the appearance /312
of gastric ulcerations in only 44% of the adrenalectomized animals and the reduction in the ulcerated surface to 0.9 $mm^2$ is not so much an expression of the participation of these glands in producing ulcerations as it is an expression of a general /313
reduction in the reactivity of the organism deprived of corticosteroid secretion in the ensuring of its homeostasis.

Our data differ from those of Brodie [7] and Martindale [12], who observed an increase in the number of animals with gastric ulcerations after immobilization for 24 hours under conditions of adrenalectomy, but agree with those of Bonfils et al. [5], who observed that adrenalectomy did

Fig. 9. Microscopic appearance of gastric ulcerations.

did not alter the percentage of animals with gastric ulcerations after immobilization for 7 hours. A general drop in the organism's defensive capacity is also supported by the fact observed by Brodie [7] that these animals had the highest mortality rate. By the same token, we believe that this hypothesis is also supported by the results obtained through administration of cortisone. Although it fostered the appearance of ulceration in all the animals, cortisone reduced the ulcerated surface and increased the resistance of the rats, all of which survived after immobilization for 24 hours. Bonfils et al. [5] believe that the action of cortisone depends on the manner of administration: administered parenterally, cortisone reduced the incidence of gastric ulceration slightly whereas administered per os it did not exert any effect. We believe that the reduction in the number of animals with ulcerations observed by Bonfils et al. can be explained by the shorter duration of immobilization time (7 hours in the experiments of Bonfils et al. and 24 hours in ours).

As a matter of fact, a reduction in the ulcerated surface through cortisone was also noted by some of us on the occasion of other studies on Shay's ulcer or through double nephrectomy [14]. We have been inclined to consider that the effects of cortisone are due to its anti-inflammatory action and perhaps to the drop in vascular permeability, which thereby increases the gastric mucosa's resistance to those factors which tend to increase the number of ulcerations.

Finally, our interpretation is also supported by the investigation of urinary elimination of corticosteroids. The reduction in elimination of glycocorticoids, whose ulcerogenic action is well known, shows that the ulcerations observed in our experiments could not have been due to an increase in secretion of these hormones. The simultaneous reduction in urinary uropepsin, whose elimination is increased by cortisone, also argues against increased production of glycocorticoids under the influence of forced immobilization.

Further, Knigge et al. [11] found that immobilization does not lead to depletion of antihypophysin in ACTH, a fact which might explain the absence of increased production of 17-hydroxycorticosteroids.

On the other hand, we wonder whether the increased elimination of 17-ketosteroids which was observed in some cases but which was not significant for the group as a whole, a fact noted also by Simler et al. [16], is not due to hyperfunctional activity of the testicles, which still remains to be proved, of course. Let us also mention that the data on the action of sex hormones on gastric changes produced by immobilization are contradictory [10].

In conclusion, on the basis of our experiments and in agreement with Rossi and Bonfils [15], we can assume that the production of ulcerations through immobilization has a psychogenic origin, without being able to make explicit the mechanism by means of which disorders of the central nervous system lead to the appearance of lesions of the gastric mucosa.

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